REMARKS

Claim Amendments

Upon entry of the foregoing claim amendment, claims 1-8 and 15-22 will be pending. Claims 23-24 have been canceled herein without prejudice or disclaimer to the subject matter claimed therein. Claims 7, 15, 18 and 22 are currently amended. No new matter is added as a result of this amendment. Support for the amendment to the claims may be found throughout the specification (considered as a whole) and in the claims as originally filed. Applicants respectfully request entry of the above amendment and submit that the amendment does not introduce new matter.

Statement of Substance of Interview Under 37 C.F.R. § 1.133(b)

In accordance with 37 C.F.R. § 1.133(b) and M.P.E.P. § 713.04, Applicants provide a summary of the interview between Applicants, Applicants' representatives and Examiner Prouty conducted on January 15, 2008 ("the interview"). Applicants thank Examiner Prouty for agreeing to conduct the interview and appreciate the courtesies extended by the Examiner.

During the interview, Applicants asserted that it would not have been obvious to one of ordinary skill in the art to apply the method of Blakesley to an *in vitro* transcription and translation ("ITT") system. Applicants explained, *inter alia*, that while pyrophosphorolysis inhibits DNA synthesis methods such as PCR and DNA sequencing, it is not problematic for transcription. Furthermore, Applicants pointed out that because the only type of nucleic acid synthesis involved in an ITT system is transcription, prevention of pyrophosphorolysis through the method of Blakesley would be an entirely ineffective means of enhancing the claimed invention. Examiner Prouty agreed that this argument is convincing, subject to verification that the Blakesley reference does not explicitly suggest application of his method to transcription.

Objection to the Specification

The Office Action objects to the specification because the abstract does not commence on a separate sheet. Applicants provide the abstract herewith on a separate sheet. Accordingly, Applicants respectfully submit that the objection to the specification is moot. Applicants have also amended the specification to provide a cross-reference to related applications.

Objections to the Claims

The Office Action objects to claims 22 and 23 under 37 C.F.R. § 1.75 as being substantial duplicates of claim 15 and to claim 24 as being a substantial duplicate of claim 1. Claims 23 and 24 has been canceled. Claim 22 has been amended to include "NTPs, DNA, and RNA polymerase." Accordingly, Applicants respectfully submit that the Examiner's objection is now moot.

The Office Action also objects to claim 7 on the grounds that the recitation of "in a cell free system" should be replaced with "in the cell-free system." As per the Examiner's suggestion, Applicants amended claim 7 to recite "in the cell-free system."

In view of the foregoing, Applicants submit that the objections to the claims are moot.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 18 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite over the recitation of "wherein extra ATP-sulfurylase is expressed by a prokaryotic organism."[1] Applicants have amended claim 18 to recite, "wherein the ATP-sulfurylase was obtained by expression from a prokaryotic organism ... or is purified." In view of the foregoing, Applicants respectfully request withdrawal of the indefiniteness rejection over claim 18.

Rejection Under 35 U.S.C. 103(a)

Claims 1-8 and 15-24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Blakesley et al. (WO 98/22615) ("Blakesley") in view of Swartz et al. (WO 0055353) ("Swartz").

The Examiner asserts that Blakesley teaches that nucleic acid synthesis may be enhanced by the addition of ATP sulfurylase. Office Action, page 5. The Examiner explains that ATP sulfurylase operates by using up the excess pyrophosphate in the system, thereby inhibiting pyrophosphorolysis (a process that works antagonistically against successful nucleic acid synthesis). Office Action, pages 5-6. The Examiner reasons that because the ITT system of Swartz involves nucleic acid synthesis (i.e., RNA synthesis as part of the transcription process), a skilled artisan would be motivated to use Blakesley's method for enhancing nucleic acid

[1] Applicants note that the Office Action suggests that claim 12 is also rejected under 35 U.S.C. 112, second paragraph. However, this appears to be a typographical error as no specific rejection of claim 12 is present in the Office Action.

synthesis reactions to improve the ITT system of Swartz. Office Action, page 6.

Applicants respectfully disagree and traverse this rejection. As an initial matter, Applicants point out that Blakesley does not teach or suggest applying his methods to RNA transcription. Applicants also maintain that one of ordinary skill in the art would have known that the addition of ATP sulfurylase, as taught by Blakesley, would not enhance RNA transcription — the type of nucleic acid synthesis performed in an ITT system. Indeed, as discussed below, the method of Blakesley is directed to preventing problems caused by pyrophosphorolysis during specific nucleic acid synthesis methods (e.g., DNA amplification and sequencing).[2] One of ordinary skill in the art would therefore not have used the method of Blakesley to enhance an ITT system because it was known that pyrophosphorolysis does *not* adversely interfere with RNA transcription. Accordingly, the method of Blakesley is irrelevant to the claimed invention.

Blakesley teaches that pyrophosphorolysis is problematic for two types of nucleic acid synthesis reactions: 1) reactions that depend upon primers and 2) reactions that depend upon the incorporation of dideoxynucleotides to terminate the extension of a growing polynucleotide chain. *See* Blakesley, page 1, line 12 to page 2, line 14; *see also id.* at page 4, lines 1-3. For example, in PCR reactions, which require primers for chain extension, pyrophosphorolysis is detrimental because the removal of nucleotides from the primer oligonucleotide may result in degraded primers that are not capable of supporting multiple rounds of DNA amplification. *See* Blakesley, page 1, lines 13-27.

Pyrophosphorolysis is similarly problematic in DNA sequencing reactions that depend upon the incorporation of dideoxynucleotides that prevent further chain extension. *See* Blakesley, page 1, line 22 to page 2, line 14. In DNA sequencing reactions, an accurate sequence may only be determined if, for each type of nucleotide (i.e., "A," "T," "G," and "C"), there are sufficient amounts of polynucleotides that terminate at each instance of a given nucleotide type to generate a detectable band on a sequencing gel. *Id.* Pyrophosphorolysis may interfere with sequencing by removing the dideoxynucleotides that have terminated chain

[2] *See, e.g.*, page 4, lines 1-3 ("In particular, the present invention may be used in primer extension reactions to prevent the inhibition of nucleic acid synthesis during amplification and may be used to prevent band drop in sequencing reactions."); *see also* Examples 1-3 disclosing the use of various agents to eliminate pyrophosphorolysis in DNA sequencing.

extension, thereby allowing further polymerization by DNA polymerase. *Id.* This may have the effect of causing certain bands on a sequencing gel to reduce their intensity or disappear altogether. *Id.* If these "drop-out" bands are not detected during analysis of the sequencing gel, an incorrect sequence for a given DNA molecule will be determined. *Id.*

Although pyrophosphorolysis is detrimental to the nucleic acid synthesis of DNA in sequencing or PCR amplification reactions, pyrophosphorolysis is irrelevant to RNA transcription. Indeed, unlike the DNA synthesis used in PCR or sequencing, RNA transcription is not dependent upon primers or the incorporation of dideoxynucleotides, which may be harmed by pyrophosphorolysis.[3] As a result, pyrophosphorolysis is not an inhibitory event in the context of transcription, the type of nucleic acid synthesis used in an ITT system. Therefore, Applicants submit that the method of Blakesley is inapplicable to the claimed invention. and that one of ordinary skill in the art would have no reason to combine the teachings of Swartz with Blakesley.

In view of the foregoing, Applicants respectfully request withdrawal of the obviousness rejection.

[3] To the extent that pyrophosphorolysis may take place during transcription, the ultimate product of transcription, a complete RNA molecule, is unaffected by the pyrophosphorolysis event. For example, if pyrophosphorolysis occurs during RNA transcription, the RNA polymerase will simply remove a single ribonucleotide. The RNA polymerase may then immediately resume the "forward" polymerization reaction, extending the RNA molecule being transcribed until an appropriate termination sequence is reached. Accordingly, pyrophosphorolysis does not adversely affect transcription.

CONCLUSION

All of the stated grounds of rejection have been properly traversed. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that the rejections be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

The Examiner is respectfully requested to contact the undersigned by telephone at the below listed telephone number in order to expedite resolution of any issues and to expedite passage of the present application to issue, if any comments, questions, or suggestions arise in connection with the present application.

No fees are believed due in connection with this response. However, if the USPTO determines that any fees, including fees for the extension of time, are due, the Commissioner is hereby authorized to credit or debit any such variance to the undersigned's **Deposit Account No. 50-0206**.

Respectfully submitted,

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Date: January 16, 2008

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